Conclusion: hTERT transcription up-regulated by E6 through the increase of c-Myc and HIF-1α strongly supports our previous studies indicating that HPV 16/18 infection could be involved in lung tumorigenesis. hTERT mRNA may be an independent prognostic factor in lung cancer, especially in HPV 16/18 E6 positive lung cancer.

PD2-2-2 **Molecular Pathology, Tue, 16:00 - 17:30**

Identification of differentially expressed genes in the course of lung adenocarcinoma development.

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Background: In 1999, WHO defined atypical adenomatous hyperplasia (AAH) as preinvasive lesion of adenocarcinoma. Recently, we developed two immortalized cell lines of AAH (PL16T) and its counterpart, bronchial epithelium (PL16B) by transfection of SV40 large T antigen (Shimada A et al, Cancer Sci. 96:668-675,2005). Using the two cell lines, differentially expressed genes in AAH cells were screened by cDNA microarray analysis.

Methods: Total RNA was extracted from PL16T and PL16B, respectively, and examined using cDNA microarray (CodeLink Human Whole Genome Bioarray, GE Health Care, USA) To confirm the differences in expression levels of genes selected by cDNA microarray analysis, quantitative real-time PCR (qRT-PCR) assay were carried out using PL16T and PL16B. Then, the expression differences of the selected genes were further examined using total RNA extracted from 24 small sized adenocarcinomas (less than 2 cm in diameter) by qRT-PCR assay. The 24 small sized adenocarcinomas contained 7 in situ adenocarcinomas (Bronchioloalveolar carcinoma (BAC); type A and B), 14 early invasive adenocarcinomas (mixed adenocarcinoma with BAC component; type C) and 3 poorly differentiated adenocarcinomas.

Results: Totally, the expression level of 30298 genes was compared between PL16T and PL16B and fourteen genes were expressed 7 times or more in PL16T than PL16B. Among the 14 genes, we succeeded to compare the expression differences of 7 genes between the two cell lines by qRT-PCR and selected two genes that were expressed 10 times more in PL16T thanPL16B. The two genes are Sushi domain containing 2 (SUSD2) and Neuromedin U (NUM). About the two genes, we examined their expressions using 24 small sized adenocarcinomas by qRT-PCR. SUSD2 was expressed significantly more in situ adenocarcinomas than normal lung tissue (p=0.022), but decreased in early invasive adenocarcinoma (p<0.01). On the other hand, NMU expression was gradually increased according to the malignant progression from in situ carcinoma to early invasive adenocarcinoma, It was expressed significantly more in early invasive adenocarcinoma than normal lung tissue (p=0.043).

Conclusions: Using immortalized AAH and normal cell lines and cDNA microarray, we detected two specific genes (SUSD2 and NMU) that express differentially between early adenocarcinoma and normal tissue. The expression pattern of SUSD2 and NMU in early stage adenocarcinoma was different. SUSD2 expression is thought to be related to carcinogenesis, but NMU expression may be associated with malignant progression.

PD2-2-3 **Molecular Pathology, Tue, 16:00 - 17:30**

Prognostic significance of L1 cell adhesion molecule (CAM) expression in pulmonary neuroendocrine tumors

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Background: Pulmonary neuroendocrine tumors (NET) are a distinct subset of tumors composing approximately 20% of all lung cancers. Although they are classified into different categories in 2004 World Health Organization (WHO) system, their clinical characteristics are variable and range from indolent to aggressive. This study was conducted to investigate the clinical value of L1 cell adhesion molecule (CAM) in pulmonary NE tumors.

Methods: We retrospectively analyzed L1-CAM expression in 71 cases of pulmonary NE tumors with diverse histological types by immunohistochemistry with monoclonal antibody A10-A3 (manufactured by HJ Hong). We evaluated the correlation of L1-CAM expression with WHO classification and various clinicopathological factors, including overall survival.

Results: L1 immunoreactivity was detected in 49 (69%) of all 71 pulmonary NE tumors. L1-CAM immunoactivity was detected in 2 (13.3%) of 15 typical carcinoids, 5 (71.4%) of 7 atypical carcinoids, 27 (81.8 %) of 33 large-cell neuroendocrine carcinomas, and 15 (93.8%) of 16 small cell lung carcinomas, respectively. The percentage of L1-CAM expression increased with the aggressiveness and progression of tumors. With median 2.6 years (range: 0.03-10.9) of follow-up duration, the 5-year overall survival rates were 81.9% (n=18) for L1-CAM negative group, 69.2% (n=9) for 1+ group, 47.1% (n=8) for 2+ group and 31.6% (n=6) for 3+ group, respectively (P<0.001, log-rank test). In multivariate analyses, age >55 years (P=0.007, HR 3.754, 95% CI= 1.261-11.180) and high L1-CAM expression greater than 20% (P=0.008, HR=2.893, 95% CI=1.255-6.669) were statistically significant independent poor prognostic factors. The high L1-CAM expression group (≥20% of the carcinoma cells stained) demonstrated an approximately 3-fold increased risk of death over patients with low L1-CAM expression group (<20% of tumor cells stained). Patients in locally advanced disease stage (P=0.002, HR=3.835, 95% CI=1.612-9.123) and advanced stage (P<0.001, HR=13.001, 95% CI=4.355-38.808) also had significantly poor prognosis over patients with localized stage of pulmonary NET.

Conclusion: These results suggest that L1-CAM immunoreactivity may be useful as diagnostic and prognostic marker in pulmonary neuroendocrine tumors.